Written Comments to the EPA Science Advisory Board
on October 25, 2010 Draft Report
Submitted by the Inorganic Arsenic Cancer Review Work Group

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These comments are submitted on behalf of the US Small Business Office of Advocacy (Advocacy) with regard to the October draft report submitted by the Inorganic Arsenic (iAs) Cancer Review Work Group. Advocacy submitted comments in June regarding the May draft report. This Work Group was convened in order to present additional recommendations on the implementation of certain key 2007 Science Advisory Board (SAB) recommendations regarding the draft 2005 "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)." This draft assessment includes an evaluation and characterization of the potential cancer hazard of inorganic arsenic and a quantitative dose-response cancer assessment for iAs.

The SAB can approve this draft report with minor revisions and relinquish its role as an independent check on EPA science assessments, or alternatively, it can send this back to the Work Group for an additional effort as described below.

EPA did not seek a comprehensive review of the draft arsenic assessment, rejected requests to expand the charge, and, in the end, did not obtain a comprehensive review from this Work Group. The Agency inexplicably chose procedures that individually and collectively had the effect of minimizing the opportunity for a true and robust independent review of even the limited issues specified in EPA's "focused" charge to the work group.

Based on the May and October draft review comments and the discussion at the Work Group meeting on April 6 and 7, Advocacy finds little evidence that the Work Group seriously considered the significant objections to the EPA Assessment raised by the public presenters at the April 6th Work Group or June 14th SAB meetings. Not one commenter supported the EPA Assessment at either forum. These presenters were among the most knowledgeable arsenic scientists in the country.

Nonetheless the SAB Work Group reports that it is responding to the SAB and public comments (see page 4 of the October draft). Despite this statement, Advocacy is unable to verify that this, in fact, did occur with respect to several key issues. These issues appear to have been overlooked or handled inadequately.

In the name of completeness and transparency, given the large public policy implications, and the large controversy surrounding this proceeding, it would be very helpful if the SAB explicitly responded to the very significant public comments, namely those surrounding the dose-response modeling, sensitivity analyses and the epidemiological literature. We suggest specific examples of additional clarifying text which appear below.

Furthermore, we are concerned, to the extent these issues were not overlooked, that the Work Group made these determinations on these important issues without a public proceeding to discuss these issues. As we understand the rules, the SAB Work Group is subject to the full transparency rules under FACA, which requires that all deliberations

are to be made in public meetings. Did the editing of the May report require no deliberation – everyone was in agreement on all key points? How did the Work Group members individually determine the appropriate answers to these difficult scientific questions without a public review? An additional public meeting to discuss the changes to the May draft would help resolve doubts about the adequacy of the new review, and potentially allow the Work Group to enter into a constructive dialogue with some of the country's most informed arsenic experts. Such a meeting could lead to a more complete and transparent report, than the current October draft report. Instead of asking the full SAB to approve this report after deliberation on November 22, it would be preferable for the SAB to instruct the Work Group to resume its deliberations at a public session.

The SAB members expressed concern at the June meeting that the Work Group did not go beyond the original SAB charge, and the new October draft clearly indicates that the Work Group review was a focused review, and that, more importantly, the Work Group did not review the new cancer slope. Given that the Assistant Administrator of the Office of Research and Development assured stakeholders that the SAB was free to expand the charge questions, the Work Group could re-visit this initial decision.

I. Background

Advocacy commented on the arsenic cancer assessment as early as 2001, when EPA initially considered lowering the drinking water standard from 50 ppb to 10 ppb.[1] At that time, we expressed concern that the evidence supporting a significant risk below 50 ppb was in substantial question. In the last ten years, much evidence has come forth supporting a drinking water threshold effect at greater than 50 ppb. This was demonstrated by the scientists who testified at the April 6th work group meeting regarding the international evidence from the U.S., Southwestern Taiwan, Chile and Argentina, the meta analysis by Mink et al., and the mode of action literature supporting a drinking water threshold. If EPA finalizes this new cancer potency factor, it will increase the cancer potency factor by a factor of 7 compared to the drinking water standard slope, and a factor of 17 over the current IRIS potency figure.

A. Impact of Revision of Arsenic Cancer Slope Factor

Why does this matter to small businesses? A change of the cancer potency (or cancer slope factor) would substantially raise the number of small water systems required to spend substantial resources to lower arsenic concentrations without any potential benefits. It also would substantially affect the number and cost of Superfund cleanups involving arsenic, a naturally occurring metal in the soil. Furthermore, it could raise unnecessary public concerns about whether the food supply can safely contain small traces of arsenic. Therefore, small businesses have a large stake in EPA using the best science.

[1] Letter from Susan Walthall, Acting SBA Chief Counsel for Advocacy, to EPA Administrator Christine Whitman, dated March 27, 2001.

B. History of Arsenic Review

EPA completed a review of inorganic arsenic in 2005, and has been working since 2007 to implement the very significant recommendations of the June 2007 SAB report. In February 2010, after an almost three year delay in updating the 2005 report, EPA issued a new draft report for review. However, instead of allowing a full review of this report, and an adequate time frame, after a three year delay, EPA suddenly announced a "focused review" of several narrow issues, and permitted the public barely more than one month to review the 575 page IRIS assessment. It denied requests to allow more time or to allow a more comprehensive review. After years of delay, we are baffled regarding EPA's justification for this truncated public review. As discussed above, the Work Group has now produced two draft reports for the full SAB's consideration.

II. The Work Group Review Suffers from Many Procedural Deficiencies.

Advocacy's earlier June comments provide a complete review of the procedural deficiencies of the SAB review process. EPA rushed through the earlier review process, and provided less than a month to review the latest draft.

III. The Work Group Failed to Provide Independent and Robust Advice to the EPA on the Key Issues.

The Office of Research and Development (ORD) requested that the SAB evaluate and comment on EPA's interpretation and implementation of the key 2007 SAB recommendations. ORD requested a review focusing in three areas of the draft cancer assessment of inorganic arsenic: evaluation of epidemiological literature, dose-response modeling approaches, and the sensitivity analysis of the exposure assumptions used in the risk assessment.[2] In our June comments, Advocacy addressed several inadequacies in the May version. The October version is not significantly improved on the points that we addressed.

The SAB should consider asking the Work Group to hold one additional public proceeding, as discussed above. Rather than adding more burden to the SAB's task by introducing additional new science to consider, Advocacy believes that it would be very instructive for the SAB to simply consider the following suggested improvements to the Work Group report in its November 22nd discussion.

[2] 94 Fed. Reg.27553, 27554 , May 17, 2010.

IV. Suggested Improvements in the Work Group Report for Completeness, Objectivity and Transparency.

In order to present a more complete, objective and transparent SAB report, the SAB needs to replace or supplement the following text, with the suggested or similar text below. We have excerpted the relevant section of the new draft October text. The suggested revised and improved sections appear beneath it in italics. The Work Group should refer to the many public comments as support for the revised text, and use those comments to further improve the suggested text.

A. Epidemiological Literature

Page 7:

> As noted by public comments, the SAB agrees that failure to control potential confounders or misclassification of study population exposure levels may bias study results. In the presentation of one of the critical epidemiology studies (Chen et al. 1992), the IRIS assessment (p.38) states, "a weakness of the study is the assumption that an individual's arsenic intake remained constant from birth to the end of the follow-up period; this flaw possibly led to the underestimation of risk." Other epidemiological studies also had similar issues. Indirect measures of individual exposure were used to estimate population exposure levels for all of the epidemiology studies. In Section 4.1, the narrative presenting the epidemiology studies should include a more detailed discussion of bias including literature citations addressing the potential for bias, both underestimating and overestimating of risk, due to confounders or limitations in exposure estimation. Emphasis should be given to estimating the quantitative consequences of any bias. While the existence of bias can usually be proposed with some certainty, the key issue is whether the quantitative consequences of bias are of sufficient magnitude to be of concern. Methods are available for this purpose (see, for example: Lash, Fox, and Fink: *Applying Quantitative Bias Analysis to Epidemiological Data*, Springer, 2009). The SAB suggests that the IRIS assessment include a simple table that identifies potential biases (misclassification of exposure, misclassification of disease, omitting confounders, etc.) and the potential magnitude and direction of bias in inferences that are drawn from the study data. A simple summary could then relate these sources of bias to their impact in the data and methods used in the IRIS assessment.

Page 7 - Suggested Revision (italicized text added):

> The SAB suggests that the IRIS assessment include a simple table that identifies potential biases …. used in the IRIS assessment.

However, EPA needs to include discussion of several other studies which suggest that exposure misclassification and reliance on median well concentrations and a comparison population as the exposure measures could be the primary cause of the positive slope factor for low dose exposure. These studies provide evidence that the calculated cancer slope at low doses arises from sources other than arsenic. Indeed, alternative models based on the low dose villages strongly suggest that there is no increasing (and possibly a flat or decreasing) slope in the dose-response curve at low dose (approximately below 100- 200 ug/L). Such a result is consistent with many other epidemiological studies. EPA also needs to explain on page F-7 why it is not appropriate to use alternative models that do find "insignificant or negative dose-response" relationships.

Page 8 Mode of Action Literature:

The SAB agrees that there are multiple potential mechanisms for arsenic carcinogenicity and potential target tissues which make it very difficult to do a single risk assessment model. This complexity and limited understanding of the mode-of-action of arsenic should be openly acknowledged in the 2010 draft IRIS assessment. While there is an ever increasing literature on arsenic, there is not enough information in the literature to definitively describe a mode-of-action for all of the multiple cancer endpoints of relevance for this assessment. The SAB notes that it is a reasonable hypothesis that bladder cancer is the result of repeated cell injury, cell death and compensatory proliferation; but there is not enough specific data at this point to confirm the hypothesis, nor are there hypotheses to explain the role of arsenic in lung cancer. For these reasons, the SAB concurs with EPA's rationale for choosing a linear default approach for risk assessment.

Page 8 - Suggested Revision (italicized text)

The SAB notes that it is a reasonable hypothesis that bladder cancer is the result of repeated cell injury, cell death and compensatory proliferation; but there is not enough specific data at this point to confirm the hypothesis. *The toxicological evidence on arsenic and bladder cancer support the non-linear model with a dominant explanation of repeated cell injury, cell death and compensatory proliferation as the mechanism. The toxicological evidence for a specific mechanism for a nonlinear explanatory model for arsenic and lung cancer has not yet developed. The epidemiological evidence supports the non-linear model for arsenic and bladder cancer (with the current exception of the NE Taiwan data) and for arsenic and lung cancer (including the NE Taiwan data). However, given the lack of definitive evidence for a specific mechanism for both lung and*

bladder cancer, the SAB concurs with EPA's rationale for choosing a linear default approach for risk assessment.

B. Sensitivity Analyses

Page 9:

The 2007 SAB recommended that EPA perform a sensitivity analysis of the Taiwanese data with different exposure metrics, with the subgroup of villages with more than one well measurement and using a multiplicative model that includes a quadratic term for dose. The SAB finds that the sensitivity analysis of dose-response modeling presented in the 2010 IRIS assessment was responsive to the previous 2007 SAB recommendations. Specifically, EPA was asked to evaluate a model using a quadratic term for dose. EPA evaluated the differences between a linear model and three non-linear models: quadratic, quadratic exponential and linear exponential. Results are described on p. 143, which concludes that "within the range of exposures covered by the epidemiological data, the alternative forms predict very similar risks." It would be very helpful if the results could be shown graphically, e.g., by showing the dose-response data and model dose-response curves for selected endpoints and age and gender classes. The SAB agrees with the conclusion that none of the alternative models materially changed the estimated risk levels versus use of a linear model. The EPA also evaluated whether the models were inordinately affected by the high end of the dose-response curve. They were not. This was evaluated by running the models without the highest exposure group. EPA evaluated whether exclusion of a reference population influenced the dose-response curve. Results of this analysis (see Fig. 5-2) suggest that exclusion of the reference population did have an effect on risk estimates. EPA evaluated the pros and cons of including a comparison population in a 2005 issues paper (Issue Paper: Inorganic Arsenic Cancer Slope Factor, Final Draft, July 23, 2005). The SAB recommends that the rationale from the issue paper be included in the draft IRIS assessment, and the reference population described in greater detail. This will provide more transparency and strengthen the scientific rationale for the agency's selection process.

Page 9 – Revision (see italicized text added):

Results of this analysis (see Fig. 5-2) suggest that exclusion of the reference population did have an effect on risk estimates. *Indeed, removal of the reference population and substitution of the nonlinear threshold changes the slope from a positive slope to a flat or negative slope in the low dose range. This needs to be transparently explained to the reader.*

Furthermore, care has to be taken such that the comparison population data does not overwhelm the analysis. In EPA's analysis, the cancer slope is only mildly influenced by the low dose villages, but 98 percent of the weight is assigned to the single point represented by the comparison population. This also needs to be transparently explained to the reader.

EPA evaluated the pros and cons of including a comparison population in a 2005 issues paper (Issue Paper: Inorganic Arsenic Cancer Slope Factor, Final Draft, July 23, 2005). The SAB recommends that the rationale from the issue paper be included in the draft IRIS assessment, and the reference population described in greater detail. This will provide more transparency and strengthen the scientific rationale for the agency's selection process.